REMARKS

Claims 1-3, 6-7, 11-19, 22-23, 26-39, 42-43, and 44-57 are pending in the above-identified application and remain for consideration. Claims 4-5, 8-9, 20-21, 24-25, 40-41 and 43-44 have been cancelled by this amendment without prejudice to Applicant. Claims 52-57 have been added by this amendment.

Claims 1-6, 8-13, 15-22, 25-29, 31-41, 43-48, and 50-51 were rejected under 35 U.S.C. § 102(b) as anticipated by PCT Published Patent Application No. WO 95/35390 by Zhang ("Zhang '390") as evidenced by U.S. Patent No. 6,168,922 to Harvey et al. ("Harvey et al. '922"), U.S. Patent No. 5,939,259 to Harvey et al. ("Harvey et al. '259"), or U.S. Patent No. 5,763,185 to Collis et al. ("Collis et al. '185").

Claims 1-3, 6, 10-13, 15-19, 22, 26-29, 31-32, 34-36, and 50-51 were rejected under 35 U.S.C. § 102(a) and § 102(e) as anticipated by Harvey et al. '922 or in the alternative as anticipated under 35 U.S.C. § 102(b) by Harvey et al. '259 as defined by A Akane et al., "Identification of the Heme Compound Copurified with Deoxyribonucleic Acid (DNA) from Bloodstains, a Major Inhibitor of Polymerase Chain Reaction (PCR) Amplification," Forensic Sci. 39: 362-372 (1994) ("Akane et al. (1994)").

Claims 37-39 and 46-47 were rejected under 35 U.S.C. § 102(a) and § 102(e) as anticipated by Harvey et al. '922 or in the alternative under 35 U.S.C. § 102(b) as anticipated by Harvey et al. '259 as evidenced by Collis et al. '185 and as defined by Akane et al. (1994).

Claims 1-6, 8-13, 15-22, 24-29, 31-41, 43-44, 46-48, and 50-51 were rejected under 35 U.S.C. § 102(b) as anticipated by PCT Published Patent Application No. WO 93/03167 by Sigman et al. ("Sigman et al. '167") as evidenced by Harvey et al. '922, Harvey et al. '259, or Collis et al. '185.

Claims 7, 23, and 42 were rejected under 35 U.S.C. § 103(a) as unpatentable over "Harvey et al." The Office Action did not state explicitly which of the two "Harvey et al." references were intended. Presumably this rejection is meant to be over Harvey et al. '922 as applied previously to these claims.

Claims 14, 30, and 45 were rejected under 35 U.S.C. § 103(a) as unpatentable over Zhang '390, Sigman et al. '167, Harvey et al. '922, or Harvey et al. '259 each in view of U.S. Patent No. 5,973,137 to Heath ("Heath '137").

Claim 49 was rejected under 35 U.S.C. § 103(a) as unpatentable over Zhang '390, Sigman et al. '167, Harvey et al. '922, or Harvey et al. '259 each in view of Ahern, The Scientist 9:1-5 (1995) ("Ahern (1995)").

Claims 1-16 were rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-8 of U.S. Patent No. 6,458,546 to Baker ("Baker '546").

Claims 17-48, 50, and 51 were rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-8 of Baker '546 in view of Sigman et al. '167.

Claim 49 was rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-8 of Baker '546 in view of Ahern (1995).

Claim 49 was also provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claim 19 of copending Application Serial No. 11/138,543 ("the '543 Application").

Claim 49 was further provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 12-13 and 17-18 of the '543 Application in view of Ahern (1995).

Reexamination of the application as amended, reconsideration of the rejections, and allowance of the claims remaining for consideration are respectfully requested.

This response is being filed subsequent to an interview with the Examiner on June 29, 2006. The undersigned respectfully thanks the Examiner for the courtesy of the interview.

The Examiner, by way of an Examiner Interview Summary Record mailed July 10, 2006, has requested that this response include the substance of the interview. The following summarizes the substance of the interview as required.

Primarily, Zhang '390 was discussed in relation to the claims. The Examiner indicated that allowable subject matter might be present if the claims recited concentrations of chelator and chaotropic salt ("chelator-enhancing component") that differed from the ranges of the prior art references.

Toward this end, the following steps were suggested:

(1) Review the cited references and Office Action to determine the ranges disclosed for the chaotrope and chelator in each of the references.

(2) Review Baker '546 and its prosecution history to determine the ranges claimed and allowed for the chaotrope and the chelator.

(3) Draft claims that encompass those allowed ranges plus any other ranges that were not clearly taught by the prior art.

(4) Include a table in the response indicating the ranges involved.

This has been followed in this response. The appropriate table is attached hereto as Exhibit A.

I. AMENDMENTS TO THE APPLICATION

Entry of the amendments to the application is respectfully requested. As detailed below, these amendments introduce no new matter.

The amendments to independent claims 1, 17, 37, and 49 recite the effect of the composition with respect to the suppression of interference by masking agents in the body of the claim. These effects were already recited in the preambles of these independent claims.

Additionally, the amendments to independent claims 1, 17, and 37 recite concentration ranges for the chelator(s) and chelator-enhancing component(s) that are recited in the specification at paragraph **[0011]** and **[0029]** for the chelator-enhancing component(s) and at paragraph **[0028]** for the chelator(s). The same paragraphs of the specification support the narrowed concentration ranges for the chelator-enhancing component(s) recited in new claims 52-57.

This response is being filed in accordance with recently revised 37 C.F.R. § 1.121, as set forth in 68 F.R. 38611 (June 30, 2003). If the amendment is considered to be not in compliance with recently revised 37 C.F.R. § 1.121, the Examiner is respectfully requested to contact the undersigned at her earliest possible convenience.

Accordingly, entry of the amendments to the claims is respectfully requested.

II. THE REJECTIONS UNDER 35 U.S.C. § 102

A. The Rejection of Claims 1-6, 8-13, 15-22, 25-29, 31-41, 43-48, and 50-51 Under 35 U.S.C. § 102(b) as Anticipated by Zhang '390 as Evidenced by Harvey et al. '922, Harvey et al. '259, or Collis et al. '185

Claims 1-6, 8-13, 15-22, 25-29, 31-41, 43-48, and 50-51 were rejected under 35 U.S.C. § 102(b) as anticipated by PCT Published Patent Application No. WO 95/35390 by Zhang ("Zhang '390") as evidenced by U.S. Patent No. 6,168,922 to Harvey et al. ("Harvey et al. '922"), U.S. Patent No. 5,939,259 to Harvey et al. ("Harvey et al. '259"), or U.S. Patent No. 5,763,185 to Collis et al. ("Collis et al. '185").

This rejection is respectfully traversed as applied to the amended claims.

The Office Action stated that the claims were drawn to a method of suppressing the interference of specific agents on a molecular assay of a nucleic acid containing a test sample (independent claims 1 or 17) or a method of improving hybridization of nucleic acids by suppressing specific masking agents (claim 37) comprising contacting the test sample with an amount of a divalent metal chelator and a chelator-enhancing component.

The Office Action further stated that Zhang '390 taught a method comprising adding a lysis buffer containing 2.5 to 5 M guanidine thiocyanate and 100 mM EDTA and 0.5% of a detergent to an equal volume of sample (serum) that contains nucleic acids considered to be test nucleic acids. According to the Office Action, Zhang '390 further taught subsequently adding nucleic acid amplification probes (target nucleic acid) and paramagnetic beads to the solution containing lysis buffer and nucleic acids from the sample. According to the Office Action, Zhang '390 further taught that hybridization occurred between the nucleic acid from the sample and the probes.

The Office Action further stated that Zhang '390 taught that samples for the method included whole blood, separated white blood cells, sputum, tissue biopsies, throat swabbings, urine, or serum.

Zhang '390 was conceded in the Office Action to not specifically teach inhibition of masking agents as set forth in the claim. However, according to the Office Action, Harvey et al. '259 taught that common inhibitors, such as hemoglobin, to nucleic acid amplification could be found in buccal swabs, plasma, serum, sputum, urine, or whole blood samples. Harvey '259 also allegedly taught that chaotropic salts, such as guanidine thiocyanate, could overcome the problem of hemoglobin inhibition. The Office Action further stated that, according to Collis '185, nucleic acid hybridization inhibitory substances were derived from heme or hematin that are commonly found in blood samples. Collis '185 further taught that adding chaotropic agents such as guanidine thiocyanate in samples containing inhibitors overcame this problem.

The Office Action further stated that the preambles of claims 17 and 37 were not given patentable weight. To address this, these claims have been amended such that the language from the preambles was also recited in the body of claims 17 and 37.

With respect to claims 1-6, 8-9, and 14-16, there is no teaching in Zhang '390 of suppressing interference by a masking agent such as those recited specifically in claim 1. The removal of unbound proteins, nucleic acids, or probes that might interfere with subsequent steps cannot be equated with the removal of a masking agent. There is absolutely no teaching or suggestion in Zhang '390 of the removal of a masking agent, as that term is defined in the specification and recited specifically in claim 1. The term "masking agent" in claim 1 and the other independent claims is defined specifically as "selected from the group consisting of leukocyte esterases, myoglobin and hemoglobin analogues, myoglobin and hemoglobin derivatives, myoglobin and hemoglobin oxidation products, myoglobin and hemoglobin breakdown products, ferritins, methemoglobin, sulfhemoglobin, and bilirubin." These masking agents cannot be equated to unbound

proteins or probes that might interfere with subsequent steps, as recited in Zhang '390; they are certainly not nucleic acids.

Again, the fact that Zhang '390 taught that wash buffers comprising 1-1.5 M guanidine isothiocyanate and 10 mM EDTA removed unbound proteins that might interfere with subsequent steps does not mean and cannot be equated to the removal of the compounds recited in claim 1 and other independent claims. There is no teaching in Zhang '390 or elsewhere that any of these "unbound proteins" are any of the masking agents recited in claim 1 or other independent claims.

With respect to claims 37-41 and 43-47, there is again no teaching in Zhang '390 of improvement in hybridization of nucleic acids attributable to the removal or suppression of the specific masking agents recited in these claims. Given that there is no teaching in Zhang '390 of the removal or suppression of the specific masking agents recited in these claims, there can be no basis for asserting that there is improvement in hybridization of nucleic acids attributable to the removal or suppression of these specific masking agents.

Moreover, there is no actual teaching in Zhang '390 that the use of the actual agents recited in the claims of the present application, namely the divalent metal chelator and the chelator enhancing component, is responsible for the removal of any masking agent recited in these claims. To quote Zhang '390 at page 14, lines 21-25:

> For example, a suitable lysis buffer for use in the present method comprises 2.5-5M guanidine thiocyanate (GnSCN), 10% dextran sulfate, 100mM EDTA, 200mM Tris-HCl (pH 8.0) and 0.5% NP-40 (Nonidet P-40, a nonionic detergent, N-lauroylsarcosine, Sigma Chemical Co., St. Louis, MO).

There is no teaching in Zhang '390 that either the guanidine thiocyanate or the EDTA actually removes any masking agent recited in the claims of the present

application. To assume this ignores the fact that Zhang '390 also recites the use of dextran sulfate and the nonionic detergent N-lauroylsarcosine. Therefore, there is no proof in Zhang '390 or elsewhere that any effect on any masking agent recited in the claims of the present application is not due to either or both of dextran sulfate or N-lauroylsarcosine.

To further clarify that the claims of the present invention are not anticipated by the disclosure of Zhang '390, independent claims 1, 17, and 37 are amended to recite that the concentration of chelator enhancing component(s) is from about 0.1 M to about 1.75 M, and wherein the concentration of chelator(s) is from about 0.01 M to about 0.1 M. These ranges of chelator enhancing component(s) and chelator(s) are not taught or suggested in Zhang '390, wherein the ranges of chelator-enhancing component(s) and chelator(s) are from 2.5 to 5 M of guanidine thiocyanate (chelator-enhancing component) and 100 mM EDTA (chelator) (Zhang '390, page 14, lines 23-24). Example 1 of Zhang uses 5 M guanidine thiocyanate (page 40, line 12). Newly added dependent claims 52-57 further narrow these ranges.

The comments at Paragraph 7 of the Office Action are in fact not consistent with the actual teachings of Zhang '390. The issue is not "secondary considerations," but the fact that Zhang '390 does not teach that either the guanidine thiocyanate or the EDTA actually removes or suppresses the activity of any masking agent recited in these claims. Therefore, there is in fact no showing that the teachings of Zhang '390 "would necessarily improve hybridization because the reagents and methods of Zhang are the same as those encompassed by the instantly claimed invention." The teachings of Zhang '390 do not necessarily lead to this conclusion; if this is an argument for anticipation by inherency, it falls short of the required standard.

Accordingly, the Examiner is respectfully requested to withdraw this rejection as applied to the amended claims.

B. The Rejection of Claims 1-3, 6, 10-13, 15-19, 22, 26-29, 31-32, 34-36, and

50-51 Under 35 U.S.C. § 102(a) and § 102(e) as Anticipated by Harvey et al. '922 or in the Alternative as Anticipated under 35 U.S.C. § 102(b) by Harvey et al. '259 as Defined by Akane et al. (1994)

Claims 1-3, 6, 10-13, 15-19, 22, 26-29, 31-32, 34-36, and 50-51 were rejected under 35 U.S.C. § 102(a) and § 102(e) as anticipated by Harvey et al. '922 or in the alternative as anticipated under 35 U.S.C. § 102(b) by Harvey et al. '259 as defined by A Akane et al., "Identification of the Heme Compound Copurified with Deoxyribonucleic Acid (DNA) from Bloodstains, a Major Inhibitor of Polymerase Chain Reaction (PCR) Amplification," Forensic Sci. 39: 362-372 (1994) ("Akane et al. (1994)").

This rejection is also respectfully traversed as applied to the amended claims.

The Office Action stated that the claims were drawn to a method of suppressing the interference of specific masking agents on a molecular assay of a nucleic acid containing test sample (claims 1 and 17) comprising contacting the test sample with an amount of a divalent metal chelator and a chelator-enhancing component.

The Office Action further stated that Harvey et al. '922 and Harvey et al. '259 taught and claimed methods and devices for collecting, storing, and purifying nucleic acids such as DNA or RNA from fluid samples for subsequent genetic characterization by conventional amplification methods comprising adding EDTA and guanidine thiocyanate to a test sample containing nucleic acids.

With regard to claims 31-33, Harvey et al. '922 and Harvey et al. '259 were stated in the Office Action to specifically teach that the nucleic acids can be either from an untreated source such as saliva, serum or urine, or a treated blood source that has naturally occurring nucleic acid amplification inhibitors present, such as hemoglobin.

Harvey et al. '922 and Harvey et al. '259 were stated to teach a device described as "903 paper" that is composed of an absorbent material that does not bind nucleic acids irreversibly, and is impregnated with a chaotropic salt such as guanidine isothiocyanate or sodium perchlorate. Harvey et al. '922 and Harvey et al. '259 were stated to specifically teach a method whereby a square of treated paper was added to blood which had been collected in a tube containing EDTA. Harvey et al. '922 and Harvey et al. '259 taught that DNA was extracted from the paper and subjected to PCR.

The Office Action conceded that Harvey et al. '922 or Harvey et al. '259 did not teach suppressing the effects of methemoglobin. However, the Office Action contended that such inhibition was known to be caused by heme, as taught by Akane et al. (1994), which is a component of methemoglobin.

In the first place, there is no basis for the position taken by the Office that the prior application, Application Serial No. 09/185,401 ("the '401 Application") does not provide support for the recitation of a "masking agent" in general. It is conceded that the '401 Application does recite hemoglobin and methemoglobin, which are typical masking agents as that term is used in the present specification and claims. It is well understood that not all specific examples of a compound that has a particular activity or properties be recited in the specification for there to be support for a more general recitation of a compound having such activity or properties. In re Wright, 27 U.S.P.Q. 2d 1510, 1513 (Fed. Cir. 1993) ("Nothing more than objective enablement is required, and therefore it is irrelevant whether [a] teaching is provided through broad terminology or illustrative examples.") There is nothing in the properties of hemoglobin or methemoglobin that makes them unrepresentative examples of masking agents as that term is used in the present specification and claims. One of ordinary skill in the art would therefore conclude that there was sufficient support in the specification of the '401 Application for the general recitation of "masking agents."

Accordingly, priority to the '401 Application is appropriate and the Examiner is therefore respectfully requested to reverse the prior decision and award

Applicant priority to the '401 Application. The fact that all possible masking agents are not recited in the '401 Application is not grounds for denying Applicant priority to the '401 Application. That is not the standard under the first paragraph of 35 U.S.C. § 112 either with respect to the enablement requirement or with respect to the written description requirement.

Even if priority is not granted for the '401 Application with respect to the recitation of "a masking agent" in general, Harvey et al. '922 does not teach the claimed invention because Harvey et al. '922 does not teach adding the required components to a "test sample" as that term is used in the specification and claims of the present application. The nucleic acid is applied to an absorbent such as a paper (e.g., claim 1 of Harvey et al. '922). An example is a cellulosic paper (column 3, lines 16-18). The nucleic acid must be released from the support to create a "test sample." Although the specification does not specifically define "test sample," one of ordinary skill in the art would not consider such a paper to be a "test sample" for a molecular assay such as PCR. One of ordinary skill in the art would require that the nucleic acid be released from the paper and be eluted or dissolved into a liquid medium in which PCR or other structure-specific molecular assay could be performed to form a test sample for the molecular assay. The enzymes and other reagents require such a liquid medium, typically an aqueous medium.

The fact that heme was known to inhibit PCR reactions, as taught by Akane et al. (1994), does not make Harvey et al. '922 or Harvey et al. '259 an anticipatory reference. Akane et al. (1994) tentatively identified the inhibitory component as a heme-blood protein complex. However, Harvey et al. '922 or Harvey et al. '259 does not teach or suggest the method of the invention in which specific reagents are required to be added to a test sample. A sample of nucleic acid absorbed on filter paper, as is disclosed by Harvey et al. '922 or Harvey et al. '259, is not a test sample and cannot be used for that purpose. The nucleic acid must be solubilized or otherwise removed from the filter paper before it can be used for a molecular assay as defined in the

present application. Harvey et al. '922 or Harvey et al. '259 are properly regarded as directed to storage methods.

Moreover, Harvey et al. '922 or Harvey et al. '259 lack a teaching of "an amount of a divalent metal chelator and an amount of at least one chelator enhancing component, the amounts of said divalent metal chelator(s) and said chelator enhancing component(s) being selected such that the effects of any masking agents selected from the group consisting of leukocyte esterases, myoglobin and hemoglobin analogues, myoglobin and hemoglobin derivatives, myoglobin and hemoglobin oxidation products, myoglobin and hemoglobin breakdown products, ferritins, methemoglobin, sulfhemoglobin, and bilirubin are suppressed in the molecular assay" as required by claim 1 and other independent claims. The quantities of the divalent metal chelator and the chelator enhancing component used on the storage paper in Harvey et al. '922 or Harvey et al. '259 have not been shown to be sufficient to suppress the effect of any of the listed masking agents in the molecular assay once a test sample, as that term would be understood by one of ordinary skill in the art.

To further clarify that Harvey et al. '922 or Harvey et al. '259 do not anticipate these claims, independent claims 1and 17 are amended to recite that the concentration of chelator enhancing component(s) is from about 0.1 M to about 1.75 M, and wherein the concentration of chelator(s) is from about 0.01 M to about 0.1 M. These ranges of chelator enhancing component(s) and chelator(s) are not taught or suggested in Harvey et al. '922 or Harvey et al. '259, wherein the ranges of chelator-enhancing component(s) and chelator(s) are much lower. Harvey et al. '922 or Harvey et al. '259 uses a paper impregnated with solution of between 0.1 M to 6.0 M guanidine salts, preferably from 0.5 to 2.0 M. Example 1 has a range of from 0.5 M to 5.0 M, preferably about 2.0 M. The salt can be guanidine isothiocyanate, guanidine thiocyanate, guanidine hydrochloride, sodium iodide, sodium perchlorate, potassium iodide, sodium thiocyanate, sodium isothiocyanate, urea (not really a salt), or combinations thereof.

In this context, the issue with respect to Harvey et al. '922 or Harvey et al. '259 is what is the actual concentration of chaotrope resulting in the solution produced when a filter paper containing sample and chaotrope is redissolved. One approach to that issue is to determine the concentration of chaotrope resulting from the redissolution, following Example 3. A 1/8 inch circle (not certain whether radius or diameter, assume radius) is used. 1/8 inch equals 0.3175 cm, so the area of the circle is 0.3166 cm^2. The volume of the paper in the circle, given a thickness of 0.52 mm is 0.0164 cm^3. The paper absorbs 4.5 g (effectively equivalent to 4.5 ml) of water per 100 cm^3, which means that the volume of solution absorbed is 7.38×10^{-4} ml. This is redissolved in 0.5 ml of water, so that the effective dilution is approximately 677-fold. Thus, even the maximum concentration of chaotrope used in Harvey (6.0 M) would result in an actual solution including the nucleic acid and the sample of nucleic acid yielding a concentration of chaotrope of only 8.86 millimolar. This is far below what is recited in the claims of the present application.

To further clarify this point, newly added dependent claims 52-54 further narrow these ranges.

The comments at Paragraph 9 of the Office Action do not support the position taken by the Patent and Trademark Office regarding this rejection. As clarified above, there is ample support for the claimed invention in the '401 Application, and priority from this application is appropriate. Additionally, the term "sample" cannot be equated to "test sample" without basis for equating the two terms. Language in a patent application, including both the specification and the claims, should be given its plain meaning and should not be treated as mere surplusage.

Accordingly, the Examiner is respectfully requested to withdraw this rejection.

C. <u>The Rejection of Claims 37-39 and 46-47 Under 35 U.S.C. § 102(a) and § 102(e) as Anticipated by Harvey et al. '922 or in the Alternative as</u>

Anticipated Under 35 U.S.C. § 102(b) by Harvey et al. '259
as Evidenced by Collis et al. '185 and as Defined by Akane et al. (1994)

Claims 37-39 and 46-47 were rejected under 35 U.S.C. § 102(a) and § 102(e) as anticipated by Harvey et al. '922 or in the alternative under 35 U.S.C. § 102(b) as anticipated by Harvey et al. '259 as evidenced by Collis et al. '185 and as defined by Akane et al. (1994).

This rejection is also respectfully traversed as applied to the amended claims.

The Office Action stated that the claims were drawn to a method of improving hybridization of nucleic acids by suppressing specific masking agents comprising contacting the test sample with amount of a divalent metal chelator and a chelator-enhancing component.

With regard to claims 37-39, 46, and 47, Harvey et al. '922 and Harvey et al. '259 were stated in the Office Action to teach methods and devices for collecting, storing, and purifying nucleic acids such as DNA or RNA from fluid samples for subsequent genetic characterization by conventional amplification methods. As with the rejection traversed above in Section (II)(B), Harvey et al. '922 and Harvey et al. '259 were stated in the Office Action to specifically teach that the nucleic acids can be either from an untreated source such as saliva, serum or urine, or a treated blood source that has naturally occurring nucleic acid amplification inhibitors present, such as hemoglobin.

Harvey et al. '922 and Harvey et al. '259 were stated to teach a device described as "903 paper" that is composed of an absorbent material that does not bind nucleic acids irreversibly, and is impregnated with a chaotropic salt such as guanidine isothiocyanate or sodium perchlorate. Harvey et al. '922 and Harvey et al. '259 were stated to specifically teach a method whereby a square of treated paper was added to

blood which had been collected in a tube containing EDTA. Harvey et al. '922 and Harvey et al. '259 taught that DNA was extracted from the paper and subjected to PCR.

The Office Action conceded that Harvey et al. '922 or Harvey et al. '259 did not teach suppressing the effects of methemoglobin. However, the Office Action contended that such inhibition was known to be caused by heme, as taught by Akane et al. (1994), which is a component of methemoglobin. Moreover, the Office Action conceded that Harvey et al. '922 or Harvey et al. '259 did not specifically recite improvement of hybridization by suppressing a masking agent, as evidenced by Collis '185, nucleic acid hybridization inhibitory substances were stated to be derived from heme and hematin which are commonly found in blood samples. Collis '185 was stated to teach that adding chaotropic agent such as guanidine thiocyanate in samples containing inhibitors overcame this problem.

The Office Action further stated that the preamble of claim 37 was not given patentable weight. Although Applicant respectfully disagrees and asserts under the holding of Pitney Bowes, Inc. v. Hewlett-Packard Co., 51 U.SP.Q. 2d 1161, 1165-66 (Fed. Cir. 1999), that the preamble is to be given patentable weight because it "gives life, meaning, and vitality to the claim" and makes clear what is to be accomplished by the method steps recited in the claim, to advance prosecution claim 37 has been amended to insert the language of the preamble into the body of the claim. Thus, the preamble language, now incorporated into the body of the claim, is to be considered in evaluating the patentability of the claim.

This rejection is respectfully traversed because Harvey et al. '922 or Harvey et al. '259 do not teach the subject matter of these claims as amended. Neither Harvey et al. '922 or Harvey et al. '259 discloses the improvement of hybridization resulting from the suppression of the activity of the masking agents. This is now recited in the body of the claim as explained above. Harvey et al. '922 and Harvey et al. '259 do not disclose that hybridization is improved as the result of storage or treatment.

The process disclosed in Harvey et al. '922 and Harvey et al. '259, unlike the process of the present invention, does not result in an improvement of hybridization without a physical separation of the masking agents. In the process of the present invention such as recited in claims 37-39, 46, and 47, the masking agents are not physically separated from the nucleic acid molecules that undergo hybridization. Rather, the effect of the chelator and the chelator-enhancing component is to improve the efficiency of hybridization even though the masking agents recited in these claims are not physically separated from the masking agents. This is not true of Harvey et al. '922 or Harvey et al. '259. The results reported in Examples 1-6 of Harvey et al. '922 or Harvey et al. '259 are likely to be the result of a physical separation of the masking agents from the DNA as the result of adsorption to the paper or increased concentrations of DNA being eluted from the paper.

To further clarify the conclusion that Harvey et al. '259 or Harvey et al. '922 do not anticipate the subject matter of these claims, claim 37 has been amended to recite ranges of concentrations for the chelator(s) and chelator-enhancing component(s) as for claims 1 and 17 above. Additionally, newly added dependent claims 55-57 further narrow these ranges. The argument for patentability is the same as recited above with respect to claims 1-37 and claims dependent thereon.

Therefore, Harvey et al. '259 and Harvey et al. '922 do not anticipate the subject matter of these claims.

Accordingly, the Examiner is respectfully requested to withdraw this rejection as applied to the amended claims.

D. <u>The Rejection of Claims 1-6, 8-13, 15-22, 24-29, 31-41, 43-44, 46-48, and 50-51 Under 35 U.S.C. § 102(b) as Anticipated by Sigman et al. '167 as Evidenced by Harvey et al. '922, Harvey et al. '259, or Collis et al. '185</u>

Claims 1-6, 8-13, 15-22, 24-29, 31-41, 43-44, 46-48, and 50-51 were rejected under 35 U.S.C. § 102(b) as anticipated by PCT Published Patent Application No. WO 93/03167 by Sigman et al. ("Sigman et al. '167") as evidenced by Harvey et al. '922, Harvey et al. '259, or Collis et al. '185.

This rejection is also respectfully traversed as applied to the amended claims.

The Office Action stated that the claims were drawn to a method of suppressing the interference of specific masking agents on a molecular assay of a nucleic acid containing test sample (claims 1 and 17) or a method of improving hybridization of nucleic acids by suppressing specific masking agents (claim 37) comprising contacting the test sample with an amount of a divalent metal chelator and a chelator-enhancing component.

The Office Action further stated that Sigman et al. '167 taught a method of isolating and preserving DNA. According to the Office Action, Sigman et al. '167 taught that is a need to isolate and prevent degradation of DNA in blood samples from patients suspected of infection with parasites such as *Trypanosoma cruzi* or other infectious agents during storage. With regard to claims 1-3, 6, 17-19, 22, and 37-39, the Office Action stated that Sigman et al. '167 taught that isolation and storage comprises contacting a biological sample containing DNA in cells with a buffer (aqueous solution) containing a nonamphipathic chaotropic salt (chelator enhancing component) such as guanidine thiocyanate or guanidine chloride and a concentration of a chelating agent (divalent metal chelator) such as EDTA.

The Office Action further stated with respect to claims 31-33 that Sigman et al. '167 taught that the method is suitable for use on any biological sample including human blood, urine, sputum, or lymphatic fluid.

The Office Action further stated with respect to claims 4-5, 8-9, 20-21, 24-25, 40-41, and 43-44 that Sigman et al. '167 taught that the guanidinium chloride was present in at least 3 molar concentration. The Office Action indicated that this concentration range was considered to anticipate claim 8, because the range of "about" 0.1 to 2 M recited in that claim was interpreted to encompass 3 M. Similarly, the Office Action indicated that the range of "at least about 1 M" recited in claims 9 and 25 was interpreted to encompass a minimum of about 1 M with a maximum concentration above "about 1 M" as limited by the upper limitation in claim 8, which was stated to include 3 M. The limitation that the chelating agent was present in at least 0.1 molar concentration (claims 4, 20, and 40) in the mixture of the biological sample and storage buffer (with regard to claims 5, 21, and 41) was stated to be encompassed by the teachings of Sigman et al. '167, which taught a solution that contained a divalent metal chelator in an amount of at least about 0.01 M. Sigman et al. '167 was further stated to specifically teach that human intravenous blood was freshly drawn and added to a tube containing guanidinium chloride and EDTA so that the final concentration of guanidinium chloride was 3 M and the final concentration of EDTA was 0.1 M.

This point is addressed by amendment of independent claims 1, 17, and 37 to recite specific ranges of chelator(s) and chelator-enhancing component(s), as described above. Specifically, Sigman et al. '167 discloses concentrations of guanidine chloride or guanidine thiocyanate that are at least 3 molar concentration in the mixture of the biological sample and the lysis and storage buffer. The ranges recited are less than those recited in Sigman et al. '167. This further avoids anticipation of these claims by Sigman et al. '167.

With regard to claims 17, 36, 48, 50, and 51, the Office Action stated that Sigman et al. '167 taught conducting PCR amplification on isolated DNA. The Office Action further stated that, as Sigman et al. '167 taught that there was a need to prevent DNA degradation in blood samples, the method of Sigman et al. '167 inherently improved signal response. With regard to claim 37, the method of Sigman et al. '167 was

interpreted to improve hybridization of primers to intact DNA as compared to hybridization that would occur with regard to degraded DNA.

With regard to the preamble in claims 1, 17, and 37 as well as claims 10-13 and 26-29, the Office Action stated that although Sigman et al. '167 did not specifically teach inhibition of masking agents set forth in the claim, it was considered to be a property of the method of Sigman et al. '167 as the addition of the reagents taught by Sigman et al. '167 to the sample taught by Sigman et al. '167 provides for suppression of such masking agents. The Office Action stated that, as evidenced by Harvey et al. '259, common inhibitors, such as hemoglobin, to nucleic acid amplification can be found in buccal swabs, plasma, serum, sputum, urine, and whole blood samples. Harvey et al. '259 was also stated to teach that chaotropic salts such as guanidine thiocyanate could overcome the problem of hemoglobin inhibition. The Office Action further stated that, as evidenced by Collis '185, nucleic acid hybridization inhibitory substances were derived from heme and hematin that are commonly found in blood samples. According to the Office Action, Collis '185 taught that adding chaotropic agents such as guanidine thiocyanate in samples containing inhibitors overcame this problem.

With regard to claims 17 and 37, the Office Action stated that the recitations of the preamble did not distinguish the claimed methods from those of Sigman et al. '167 because Sigman et al. '167 was stated to teach the positive process steps of the claimed method in the same order, and thus the effects recited necessarily followed.

As stated above, this rejection is respectfully traversed. The teachings of Sigman et al. '167 are directed to methods of isolating and preserving DNA, specifically DNA associated with parasites such as *Trypanosoma cruzi*.

With respect to claims 1-6, 8-9, 14-22, 24-25, and 30-36, Sigman et al. '167 does not disclose or suggest the suppression of interference by a masking agent or the improvement of a signal response in a molecular assay due to the suppression of

interference by a masking agent. The masking agents recited specifically in these claims as amended are not disclosed by Sigman et al. '167.

Sigman et al. '167 is actually directed to the use of conditions in which controlled cleavage of the highly catenated closed circular DNA of parasites such as *T. cruzi* can be accomplished. If there is suppression of interference by a masking agent or the improvement of a signal response in a molecular assay, it is strictly inadvertent and unintentional. This is particularly true in light of the fact that the masking agents recited in the independent claims of the present application, as amended, are not disclosed in Sigman et al. '167.

It is well-established in patent law that unintended anticipation is not anticipation. Tilghman v. Proctor, 102 U.S. 707 (1881). If the work of Sigman et al. '167 creates suppression of interference by a masking agent or the improvement of a signal response in a molecular assay due to suppression of interference by a masking agent, it is unintended and is not inherent in the methods disclosed by Sigman et al. '167. In other words, there is no teaching in Sigman et al. '167 of suppression of interference by a masking agent or improvement in a signal produced by a molecular assay.

The term "molecular assay" must, in light of the specification of the present application, be read to mean a molecular assay in which sequence-specific recognition, either between two nucleic acids or between a nucleic acid and a protein, plays some role. The chemical cleavage optimized in Sigman et al. '167 is not encompassed by this definition. The chemical cleavage does not involve sequence-specific recognition either between two nucleic acids or between a nucleic acid and a protein. The chemical cleavage does not involve recognition of a second nucleic acid molecule and is not catalyzed by a protein. The cleavage is catalyzed by a reagent such as a 1,10-phenanthroline-copper complex, a derivative of ferrous EDTA, or other metal-containing octahedral complexes (page 15, lines 12-25). None of these reagents includes either protein or nucleic acid.

The mere preservation of DNA for future use does not in and of itself establish that the DNA is preserved in a condition in which the specific masking agents recited in the claims of the present application are eliminated or suppressed. Unless this is done, and there is no teaching of this in Sigman et al. '167, the masking agents will interfere with a subsequent procedure such as PCR. The masking agents will neither be removed or suppressed and will remain to cause interference. The elimination or suppression of the specific masking agents recited in the claims of the present application is not shown in Sigman et al. '167.

Again, inherency cannot be established by probabilities or possibilities. Continental Can Co., 20 U.S.P.Q. 2d at 1746. Prevention of degradation by a nuclease cannot be equated with the suppression of interference with a masking agent. Most masking agents do not act to degrade the DNA.

With respect to claims 37-41 and 43-48, Sigman et al. '167 fails to teach or disclose improvement in hybridization. Again, Sigman et al. '167 is focused on methods by which the DNA is subject to chemical cleavage. There is no teaching in Sigman et al. '167 of improvement in hybridization and no discussion in Sigman et al. '167 of improvement in hybridization that can possibly be attributed to the removal or suppression of the specific masking agents recited in these claims. Again, any anticipation would be unintended and accidental, and would not be inherent in the methods of Sigman et al. '167.

The comments at Paragraph 12 of the Office Action do not support this rejection. The teaching that Sigman et al. '167 "was specifically taught to isolate and preserve the DNA for future use" does not in and of itself teach that the activity of the specific masking agents recited in these claims would be suppressed by the process of Sigman et al. '167. The preservation of the DNA could readily include the preservation of the masking agents. Moreover, it is not reasonable to interpret the term "molecular assay" as "any assay involving DNA." The thrust of the specification and claims is

clearly directed to assays that involve sequence-specific recognition of a DNA molecule, either by another nucleic acid molecule or a protein molecule.

Accordingly, the Examiner is respectfully requested to withdraw this rejection.

III. THE REJECTIONS UNDER 35 U.S.C. § 103(a)

A. The Rejection of Claims 7, 23, and 42 Under 35 U.S.C. § 103(a) as Unpatentable Over "Harvey et al."

Claims 7, 23, and 42 were rejected under 35 U.S.C. § 103(a) as unpatentable over "Harvey et al." The Office Action did not state explicitly which of the two "Harvey et al." references were intended. Presumably this rejection is meant to be over Harvey et al. '922 as applied previously to these claims. Clarification of this rejection is therefore respectfully requested.

"Harvey et al." was stated in the Office Action as teaching and claiming methods and devices for collecting, storing, and purifying nucleic acids such as DNA or RNA from fluid samples for subsequent genetic characterization by conventional amplification methods. "Harvey et al." specifically taught that the nucleic acids could be either from an untreated blood source such as saliva, serum, or urine, or a treated blood source that has naturally occurring nucleic acid amplification inhibitors present, such as hemoglobin. "Harvey et al." was stated in the Office Action to teach that the device should be composed of an absorbent material that does not bind nucleic acids irreversibly and that is impregnated with a chaotropic salt such as guanidine isothiocyanate or sodium perchlorate. "Harvey et al." was stated to specifically teach a method whereby a square of treated paper treated with guanidine thiocyanate was added to blood that had been collected in a tube containing EDTA. "Harvey et al." was stated to teach that DNA was extracted from the paper and subjected to PCR.

"Harvey et al." was conceded not to specifically exemplify paper treated with sodium perchlorate. However, "Harvey et al." was stated to teach that it would have been a suitable chaotropic agent.

This rejection is also respectfully traversed as applied to the amended claims, as no *prima facie* case of obviousness exists.

Harvey et al. '922 or Harvey et al. '259 does not teach or suggest the claimed invention because Harvey et al. '922 or Harvey et al. '259 does not teach adding the required components to a "test sample" as that term is used in the specification and claims of the present application. The nucleic acid is applied to an absorbent such as a paper (e.g., claim 1 of Harvey et al. '922). An example is a cellulosic paper (column 3, lines 16-18). The nucleic acid must be released from the support to create a "test sample." Although the specification does not specifically define "test sample," one of ordinary skill in the art would not consider such a paper to be a "test sample" for a molecular assay such as PCR. One of ordinary skill in the art would require that the nucleic acid be released from the paper and be eluted or dissolved into a liquid medium in which PCR or other structure-specific molecular assay could be performed to form a test sample for the molecular assay.

The basis of this rejection is that it would have been obvious to use the device of Harvey et al. '922 or Harvey et al. '259 treated with sodium perchlorate as a chelator enhancing component because Harvey et al. '922 and Harvey et al. '259 teach that sodium perchlorate is a chaotropic agent. Although it may have in fact been *prima facie* obvious to use the device of Harvey et al. '922 or Harvey et al. '259 treated with sodium perchlorate, this still does not teach the method of the invention. All claim limitations must be considered in evaluating the non-obviousness of an invention in light of prior art. In re Fine, 5 U.S.P.Q. 2d 1596 (Fed. Cir. 1988). As indicated above, Harvey et al. '922 or Harvey et al. '259 does not teach the use of these agents in a test sample.

Therefore, even though one of ordinary skill in the art might know that sodium perchlorate is a chaotropic agent, the combination of that knowledge with the teachings of Harvey et al. '922 or Harvey et al. '259 does not result in the claimed invention. This is because of the lack of teaching of the context of a test sample by Harvey et al. '922 or Harvey et al. '259. This must be considered in evaluating non-obviousness.

Harvey et al. '922 or Harvey et al. '259 are properly regarded as directed to storage methods and cannot be regarded as teaching the suppression of interference by masking agents in molecular assays without hindsight reconstruction using the disclosure of the present invention. Such hindsight reconstruction is proscribed in the analysis of non-obviousness under 35 U.S.C. § 103(a). Grain Processing Corp. v. American Maize-Products Co., 5 U.S.P.Q. 2d 1788, 1792 (Fed. Cir. 1988).

Moreover, Harvey et al. '922 or Harvey et al. '259 lack a teaching of "an amount of a divalent metal chelator and an amount of at least one chelator enhancing component, the amounts of said divalent metal chelator(s) and said chelator enhancing component(s) being selected such that the effects of any masking agents selected from the group consisting of leukocyte esterases, myoglobin and hemoglobin analogues, myoglobin and hemoglobin derivatives, myoglobin and hemoglobin oxidation products, myoglobin and hemoglobin breakdown products, ferritins, methemoglobin, sulfhemoglobin, and bilirubin are suppressed in the molecular assay" as required by claim 1 and other independent claims. The quantities of the divalent metal chelator and the chelator enhancing component used on the storage paper in Harvey et al. '922 or Harvey et al. '259 have not been shown to be sufficient to suppress the effect of any of the listed masking agents in the molecular assay. Obtaining the correct quantities of the divalent metal chelator and the chelator-enhancing component for use in a test sample in a molecular assay again amounts to proscribed hindsight reconstructions. Grain Processing Corp. v. American Maize-Products Co., 5 U.S.P.Q. 2d at 1788, 1792.

Therefore, the fact that Harvey et al. '922 or Harvey et al. '259 can be read as to possibly suggest the use of sodium perchlorate as a chaotropic salt by itself does not remedy the deficiencies in these references explained above. This does not provide the correct quantities of the divalent metal chelator or the chelator-enhancing component. To provide the correct quantities requires hindsight reconstruction using Applicant's own disclosure, which is proscribed.

The lack of obviousness of these claims over Harvey et al. '922 or Harvey et al. '259 is emphasized by the amendments made to claims 1, 17, and 37 to recite ranges of chaotropic salts ("chelator-enhancing component(s)") that are not taught or suggested by Harvey et al. '922 or Harvey et al. '259. As explained above, these references teach a far lower concentration of chaotropic salts than is recited in these claims because Harvey et al. '922 and Harvey et al. '259 rely on chaotropic salts that are eluted from a small square of filter paper. The concentrations of chaotropic salts eluted from the filter paper are far lower than recited in these claims as amended, and there is no teaching or suggestion in Harvey et al. '922 or Harvey et al. '259 of using higher concentrations of chaotropic salts or modifying the delivery system of the chaotopic salts so that a higher concentration of chaotropic salts could be delivered.

The comments at Paragraph 14 of the Office Action fail to support the rejection. The teaching of "an absorbent material that does not bind nucleic acids irreversibly, impregnated with a chaotropic salt such as sodium perchlorate" does not equate to a test sample for the reasons recited above.

Accordingly, the Examiner is respectfully requested to withdraw this rejection.

B. The Rejection of Claims 14, 30, and 45 Under 35 U.S.C. § 103(a) as Unpatentable Over Zhang '390, Sigman et al. '167, Harvey et al. '922, or Harvey et al. '259 Each in View of Heath '137

Claims 14, 30, and 45 were rejected under 35 U.S.C. § 103(a) as unpatentable over Zhang '390, Sigman et al. '167, Harvey et al. '922, or Harvey et al. '259 (in the alternative) each in view of U.S. Patent No. 5,973,137 to Heath ("Heath '137").

This rejection is also respectfully traversed as applied to the amended claims. It is traversed because no *prima facie* case of obviousness has been made in view of the teachings of the prior art.

Zhang '390 was stated to teach a method comprising adding a lysis buffer containing 2.5-5 M guanidine thiocyanate and 100 mM EDTA and 0.5% of a detergent to an equal volume of sample (serum) that contains nucleic acids (test nucleic acids) and subsequently adding nucleic acid amplification probes (target nucleic acid) and paramagnetic beads to the solution containing lysis buffer and nucleic acids from the sample. The Office Action noted that the final concentration of buffer would be 1.25-2.5 M of guanidine thiocyanate and 0.05 M of EDTA after addition of the lysis buffer to the serum sample. The Office Action further noted that Zhang '390 specifically taught that hybridization occurred between the nucleic acid from the sample and the probes. Zhang '390 also taught that the method can be used for detection of genetic variations in samples from patients with genetic diseases or neoplasia. The Office Action further noted that Zhang '390 specifically taught that samples for the method include whole blood, separated white blood cells, sputum, tissue biopsies, throat swabbings, urine, and serum.

The Office Action further stated that Sigman et al. '167 taught that there was a need to isolate and prevent degradation of DNA in blood samples from patients suspected of infection with parasites or other infectious agents. Sigman et al. '167 was considered by the Office Action to teach that isolation and storage comprised contacting a biological sample containing DNA in cells with a buffer (aqueous solution) containing a nonamphipathic chaotropic salt (chelator enhancing component) such as guanidine thiocyanate or guanidine chloride and a concentration of a chelating agent such as EDTA.

Sigman et al. '167, according to the Office Action, taught that the method was suitable for use on any biological sample including human blood, urine, sputum, and lymphatic fluid. Sigman et al. '167 was considered to teach performing PCR with the preserved nucleic acid.

Harvey et al. '922 and Harvey et al. '259 were considered in the Office Action to teach and claim methods for collecting, storing, and purifying nucleic acids such as DNA or RNA from fluid samples for subsequent genetic characterization by conventional amplification methods. Harvey et al. '922 and Harvey et al. '259 were considered to teach that the device, "903 paper", should be composed of an absorbent material that does not bind nucleic acids irreversibly, impregnated with a chaotropic salt such as guanidine thiocyanate or sodium perchlorate. Harvey et al. '922 and Harvey et al. '259 were considered to specifically teach a method whereby a square of treated paper (treated with guanidine thiocyanate) is added to blood which had been collected in a tube containing EDTA. Harvey et al. '922 and Harvey et al. '259 were considered to teach that DNA was extracted from the paper and subjected to PCR.

The Office Action conceded that neither Zhang '390 nor Sigman et al. '167 nor Harvey et al. '922 nor Harvey et al. '259 taught the addition of an enzyme inactivating component. However, Heath '137 was stated to teach that nucleic acid isolation and preservation methods should include anionic detergents, such as SDS or sarkosyl, in a concentration of 0.5% to 3% for the purposes of lysing cells or solubilizing proteins and lipids as well as denaturing proteins. Therefore, according to the Office Action, it would have been *prima facie* obvious to modify the method of Zhang '390, Sigman et al. '167, Harvey et al. '922 or Harvey et al. '259 to add SDS or sarkosyl.

Specifically, this rejection is respectfully traversed because the addition of an enzyme inhibitor as taught by Heath '137 does not remedy the deficiencies of the other references, Zhang '390, Sigman et al. '167, Harvey et al. '922 or Harvey et al. '259.

To clarify this distinction from the prior art, claims 1, 17, and 37 have been amended to recite concentrations of chaotropic salts ("chelator-enhancing component(s)") that are not taught or suggested by Zhang '390, Sigman et al. '167, Harvey et al. '922 or Harvey et al. '259, or by Heath '137. Heath '137 does not teach or suggest the use of chaotropic salts at all. Therefore, one cannot arrive at the claimed invention by modifying the teachings of Zhang '390, Sigman et al. '167, Harvey et al. '922 or Harvey et al. '259 by anything provided by Heath '137.

Additionally, there is no incentive provided by the art to combine the teachings of Heath '137 with those of the other references, because the teachings of Heath '137 are directed to the isolation of RNA at a low pH, less than 6, and preferably lower. This is a pH that is too low for the performance of an assay such as PCR because it is well below physiological pH and thus is not a suitable pH for the activity of enzymes such as DNA polymerase. Thus, one of ordinary skill in the art would not combine the teachings of Heath '137 with other references because the prior art does not suggest such a combination. In re Laskowski, 10 U.S.P.Q. 2d 1397 (Fed. Cir. 1989).

The deficiencies of the primary references, namely Zhang '390, Sigman et al. '167, Harvey et al. '922, and Harvey et al. '259 were explained in detail above. To summarize, Zhang '390 failed to teach that either the guanidine thiocyanate or the EDTA actually suppresses the effect of any masking agent recited in the claims of the present application. There is no showing that these ingredients actually suppress interference from these masking agents.

Sigman et al. '167 also failed to teach or suggest the suppression of the effect of the masking agents recited in the specification and claims in a molecular assay such as PCR.

The Harvey et al. references, Harvey et al. '922 and Harvey et al. '259, failed to teach the use of the reagents recited in a test sample as required by the claims.

Therefore, because the deficiencies of the primary references, Zhang '390, Sigman et al. '167, Harvey et al. '922, and Harvey et al. '259, are not overcome by the teachings of Heath '137, and because one of ordinary skill in the art has no incentive to combine the teachings of Heath '137 with those off the primary references, there is no *prima facie* case of obviousness.

Accordingly, the Examiner is respectfully requested to withdraw this rejection.

C. The Rejection of Claim 49 Under 35 U.S.C. § 103(a) as Unpatentable Over Zhang '390, Sigman et al. '167, Harvey et al. '922, or Harvey et al. '259 Each in View of Ahern (1995)

Claim 49 was rejected under 35 U.S.C. § 103(a) as unpatentable over Zhang '390, Sigman et al. '167, Harvey et al. '922, or Harvey et al. '259 each in view of Ahern, The Scientist 9: 1-5 (1995) ("Ahern (1995)").

This rejection is also respectfully traversed as applied to the amended claims. No *prima facie* case of obviousness has been made.

Zhang '390 was stated to teach a method comprising adding a lysis buffer containing 2.5 to 5 M guanidine thiocyanate and 100 mM EDTA and 0.5% of a detergent to an equal volume of sample that contained nucleic acids . The Office Action noted that the final concentration of buffer would be 1.25 to 2.5 M guanidine thiocyanate and 0.05 M EDTA.

Sigman et al. '167 was stated to teach that there was a need to isolate and prevent degradation of DNA in blood samples from patients suspected of infection with parasites or other infectious agents. Sigman et al. '167 was considered by the Office Action to teach that isolation and storage comprised contacting a biological sample containing DNA in cells with a buffer (aqueous solution) containing a nonamphipathic

chaotropic salt (chelator enhancing component) such as guanidine thiocyanate or guanidine chloride and a concentration of a chelating agent such as EDTA. Sigman et al. '167, according to the Office Action, taught that the method was suitable for use on any biological sample including human blood, urine, sputum, and lymphatic fluid. Sigman et al. '167 was considered to teach performing PCR with the preserved nucleic acid.

Harvey et al. '922 and Harvey et al. '259 were considered in the Office Action to teach and claim methods for collecting, storing, and purifying nucleic acids such as DNA or RNA from fluid samples for subsequent genetic characterization by conventional amplification methods. Harvey et al. '922 and Harvey et al. '259 were considered to teach that the device, "903 paper", should be composed of an absorbent material that does not bind nucleic acids irreversibly, impregnated with a chaotropic salt such as guanidine thiocyanate or sodium perchlorate. Harvey et al. '922 and Harvey et al. '259 were considered to specifically teach a method whereby a square of treated paper (treated with guanidine thiocyanate) is added to blood which had been collected in a tube containing EDTA. Harvey et al. '922 and Harvey et al. '259 were considered to teach that DNA was extracted from the paper and subjected to PCR.

Neither Zhang '390, Sigman et al. '167, Harvey et al. '922, nor Harvey et al. '259 was stated to teach the reagents or devices in kit format. However, Ahern (1995) was stated to teach that provided reagents and products in kit format was useful and convenient. The Office Action therefore stated that it would have been *prima facie* obvious to package the reagent of Zhang '390 or Sigman et al. '167 or the device of Harvey et al. '922 or Harvey et al. 259 in kit form for the purpose of providing convenient premade reagents.

Ahern (1995) is cited for the recitation of a kit format. Ahern (1995) does not remedy the deficiencies of the primary references, Zhang '390, Sigman et al. '167, Harvey et al. '922, or Harvey et al. '259, which all fail to teach suppression of interference by a masking agent in a molecular assay, such as the polymerase chain

reaction (PCR) assay. This is because the primary references fail to teach suppression of interference by the specific masking agents recited in this claim as amended.

Accordingly, the combination of Ahern (1995) with one or more of the primary references fails to teach or suggest the claimed invention in its entirety. For purposes of assessing patentability of a claimed invention over one or more references in terms of nonobviousness, the invention must be viewed as a whole. Jones v. Hardy, 220 U.S.P.Q. 1021 (Fed. Cir. 1984).

The comments at Paragraph 17 of the Office Action fail to support the rejection. The fact that the instructions of the kit carry no patentable weight does not lead to the conclusion that the subject matter incorporated in the kit is in fact obvious. The real issue is that the reagents included in the kit were not shown in the prior art to suppress interference by the masking agents recited in the claim.

Accordingly, the Examiner is respectfully requested to withdraw this rejection.

IV. THE OBVIOUSNESS-TYPE DOUBLE PATENTING REJECTIONS

A. The Rejection of Claims 1-16 Over Claims 1-8 of Baker '546

Claims 1-16 were rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-8 of U.S. Patent No. 6,458,546 to Baker ("Baker '546").

This rejection is respectfully traversed as applied to the amended claims.

The rejection is respectfully traversed, because claims 1-8 of Baker '546 do not recite a method of suppressing interference by a masking agent in a molecular assay. Preservation of a sample cannot necessarily be equated with suppression of interference by a masking agent, particularly with respect to the specific masking agents recited in claim 1. There can be many purposes for preserving a sample, and a sample can be preserved even though masking agents remain in the sample and would interfere with the performance of an assay such as PCR or hybridization. In fact, without a specific procedure to prevent interference from the masking agents, the masking agents, many of which are proteins as well, such as methemoglobin, would be preserved as well and thus would still be present to create interference with such assays. Therefore, the mere recitation of preservation of the sample does not, in and of itself, imply or suggest suppression of interference by a masking agent such as those recited in claim 1.

In the absence of any evidence that one of ordinary skill in the art would have equated the two, there can be no basis for an obviousness-type double patenting rejection over claims 1-8 of Baker '546. In re Kaplan, 229 U.S.P.Q. 678 (Fed. Cir. 1986); In re Longi, 225 U.S.P.Q. 651 (Fed. Cir. 1985).

The comments in Paragraph 20 of the Office Action do not support the rejection. It is not accurate to state that the claimed method steps of the instant application encompass the more narrow method steps of Baker '546. There is no teaching of suppression of a masking agent in the claims of Baker '546.

Additionally, there is no specific teaching in the claims of Baker '546 of the narrowed ranges for chelator and chelator-enhancing component (chaotropic salt) recited in these claims. The lack of specific teaching or guidance means that there is no basis for one skilled in the art to select these ranges. This also applies to the other obviousness-type double patenting rejections discussed below. The obviousness-type double patenting rejection is analogous to a rejection under 35 U.S.C. § 103 even though the rejection is not in fact made over that section of the statute. In re Braithwaite, 154 U.S.P.Q. 29 (C.C.P.A. 1967); In re DeBlauwe, 222 U.S.P.Q. 191 (Fed. Cir. 1984).

Therefore, the lack of specific teaching or guidance enabling one skilled in the art to select these ranges mandates a finding of no obviousness-type double patenting. Cf. In re Baird, 29 U.S.P.Q. 2d 1550 (Fed. Cir. 1994); In re Jones, 21 U.S.P.Q. 2d 1941 (Fed. Cir. 1992) (no obviousness under 35 U.S.C. § 103 when prior art does not provide guidance to particular species within relatively large genus disclosed by prior art).

Accordingly, the Examiner is respectfully requested to withdraw this rejection.

B. The Rejection of Claims 17-48, 50, and 51 Over Claims 1-8 of Baker '546 in View of Sigman et al. '167

Claims 17-48, 50, and 51 were rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-8 of Baker '546 in view of Sigman et al. '167.

This rejection is also respectfully traversed as applied to the amended claims.

To the extent that the amendment to claim 17 has not obviated this rejection, it is respectfully traversed, essentially for the reasons stated above with regard to the obviousness-type double patenting rejections of claims 1-8 over Baker '546. The obviousness-type double-patenting rejection is considered to be analogous to a prior art rejection under 35 U.S.C. § 103, and there is no teaching of the methods of claim 17-36, even if Baker '546 and Sigman et al. '167 are combined. As demonstrated above, Sigman et al. '167 does not disclose or suggest the suppression of interference by a masking agent or the improvement of a signal response in a molecular assay due to the suppression of interference by a masking agent specifically recited in these claims. Sigman et al. '167 does not teach the suppression of interference by the specific masking agents recited in claim 1. In fact, it is completely silent with respect to these masking agents.

As stated above, the claims of Baker '546 do not teach or suggest the suppression of interference by the specific masking agents recited in these claims. Therefore, the combination of Baker '546 and Sigman et al. '167 does not result in the claimed invention, and there is no basis for this obviousness-type double patenting rejection. Additionally, the claims of Baker '546 do not teach or suggest the specific ranges recited in these claims.

Accordingly, the Examiner is respectfully requested to withdraw this rejection.

C. The Rejection of Claim 49 Over Claims 1-8 of Baker '546 in View of Ahern (1995)

Claim 49 was rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-8 of Baker '546 in view of Ahern (1995).

This rejection is also respectfully traversed as applied to claim 49 as amended.

Ahern (1995) is merely cited for the teaching that kits are convenient and can be readily used to perform many procedures. Given that Baker '546 does not and cannot teach the suppression of the specific masking agents recited in claim 49 as amended, the mere teaching that a kit can be prepared does not remedy the deficiency of the teachings of Baker '546, as explained above.

The obviousness-type double-patenting rejection is again considered to be analogous to a prior art rejection under 35 U.S.C. § 103, and there is no teaching of the kit of claim 49, even if claims 1-8 of Baker '546 and Ahern (1995) are combined.

Accordingly, Applicant respectfully requests that this obviousness-type double patenting rejection be withdrawn.

D. The Provisional Rejection of Claim 49 Over Claim 19 of the '543 Application

Claim 49 was also provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claim 19 of copending Application Serial No. 11/138,543 ("the '543 Application").

To the extent that the amendment to claim 49 has not obviated this rejection, it is respectfully traversed.

This rejection is respectfully traversed because there is no teaching or suggestion of the suppression of the specific masking agents recited in claim 49 of the present application in claim 19 of the '543 Application. As stated above, such obviousness-type double-patenting rejections are again considered to be analogous to a prior art rejection under 35 U.S.C. § 103. The lack of teaching of the specific masking agents recited in this claim means that there is no obviousness-type double patenting.

E. The Provisional Rejection of Claim 49 as Unpatentable over Claims 12-13 and 17-18 of the '543 Application in View of Ahern (1995)

Claim 49 was also provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 12-13 and 17-18 of the '543 Application in view of Ahern (1995).

To the extent that the amendment of claim 49 has not obviated this rejection, it is respectfully traversed.

This rejection is respectfully traversed because there is no teaching or suggestion of the suppression of the specific masking agents recited in claim 49 in claims 12-13 or 17-18 of the '543 Application. As indicated before, Ahern (1995) is cited merely for the possibility of kits, but does not provide the necessary information to result in an obviousness-type double patenting situation for this claim. Again, such obviousness-type double-patenting rejections are again considered to be analogous to a prior art rejection under 35 U.S.C. § 103. The lack of teaching of the specific masking agents recited in this claim means that there is no obviousness-type double patenting.

Accordingly, the Examiner is respectfully requested to withdraw this rejection.

VIII. CONCLUSION

In conclusion, all claims remaining for consideration are novel and non-obvious over the references of record, whether considered individually or in combination. These claims are not subject to obviousness-type double patenting. Accordingly, prompt allowance of these claims is requested.

If any issues remain, the Examiner is respectfully requested to telephone the undersigned at (858) 450-0099 x302.

Respectfully submitted,

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EXHIBIT A

RANGES OF CHELATOR AND CHAOTROPE IN SPECIFICATION, BAKER '546, AND PRIOR ART

Document	Chelator	Chaotrope
Non-Prior Art		
Specification	1 mM-100 mM	0.1 M-2 M
Baker '546	1 mM-100 mM	0.1 M-2 M
Prior Art		
Zhang '390	100 mM	2.5 M-5 M
Harvey '259 & '922	None	~8.86 mM
Collis '185	None	2 M-6 M
Akane et al. (1994)	None	None
Heath '137	0.1-100 mM	None
Sigman et al. '167	≥ 100 mM	≥ 3 M
Ahearn (1995)	None	None